REMARKS

INTRODUCTORY COMMENTS:

Claims 1, 2, and 6-8 are currently pending. In the current Office Action, the Examiner has rejected the claims on the following grounds:

1. Under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey that the inventor had possession of the claimed subject matter at the time of filing;

2. Under 35 U.S.C. §112, first paragraph, as lacking enabling disclosure in the specification;

3. Under 35 U.S.C. §112, second paragraph, as indefinite; and

3. Under 35 U.S.C. §103(a) as obvious over PCT Publication WO 96/34626, in view of PCT Publication WO 92/16556 and U.S. Patent No. 5,795,862 to Frank et al.

Claims 1, 2, and 6-8 remain pending. The rejections are addressed in part by the prese3nt amendment to claim 1 and in part by the arguments that follow.

THE AMENDMENTS:

Claim 1 has been amended to specify that the composition comprises an allergen or allergen extract optionally modified by reaction with a cross-linking agent. Support for this amendment is found on page 2, lines 15 and 16, and in Preparations 1 and 2 on page 4 of the specification. Accordingly, no new matter has been entered.

THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, REGARDING THE WRITTEN DESCRIPTION:

The Examiner has rejected all claims under 35 U.S.C. §112, first paragraph, as failing to satisfy the written description requirement. The Examiner specifically states that while the pending claims recite a pharmaceutical composition that is optionally modified in some way,

there is insufficient disclosure in the specification of such a modified allergen. Applicants disagree.

As amended, independent claim 1 now specifies that the allergen or allergen extract is optionally modified by reaction with a cross-linking agent. The amended claim clearly indicates the type of modification encompassed by the claim. In particular, the claim now excludes the possibility that the term "optionally modified" could refer to modification of the amino acid sequence of the allergen as suggested by the Examiner. Moreover, cross-linking in the context of this application is a very well known process, as demonstrated by the references supplied to the Examiner in response to the last Office Action. Although only glutaraldehyde is exemplified as a cross-linking agent, it would be readily appreciated by a person skilled in the art that any suitable cross-linking agent would suffice, as is indicated in applicants' specification on page 2, lines 15 and 16. Reconsideration and withdrawal of the rejection is respectfully requested.

THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, REGARDING ENABLEMENT:

The Examiner has rejected claims 1, 2, and 6-8 on the ground that the specification does not provide enablement for a pharmaceutical composition comprising an optionally modified allergen. Applicants disagree. As discussed above, the term "modified allergen" has been replaced in claim one by the language "optionally modified by reaction with a cross-linking agent." As the Examiner has indicated in the Office Action, the specification is enabling for allergens modified by intramolecular cross-linking (see page 3, item 4, lines 1-3, of Paper No. 11).

The Examiner has also commented that the term "optionally" is unclear as it implies that the allergen need not be modified. The Examiner goes on to state that the specification requires that the allergen be chemically modified, specifically referencing page 4 of the specification. Applicants respectfully disagree with the Examiner's reading of the specification and point the Examiner's attention to the examples on page 4 of the specification. Preparation 2 describes an unmodified ovalbumin allergen, whereas Preparation 1 describes a grass pollen extract allergen chemically modified by crosslinking. Given the teaching of these two preparations, crosslinking is optional and the specification fully enables the pending claims. Reconsideration and withdrawal of the rejection is accordingly in order and is respectfully requested.

THE REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH.

The Examiner has rejected all claims under 35 U.S.C. §112, second paragraph, as indefinite, specifically rejecting claim 1 for its use of the term "optionally modified." Applicants disagree. As discussed above, claim 1 has been amended to specify that the allergen or allergen extract is optionally modified by reaction with a cross-linking agent. In the preceding discussion, applicants have amply demonstrated that modification with a cross-linking agent is fully enabled by the specification and would be understandable to one of ordinary skill in the art. The optional nature of the modification is also supported in the examples on page 4 of the specification and would be clearly understandable to one of skill in the art. Reconsideration and withdrawal of the rejection of claim 1 are accordingly requested.

THE REJECTION UNDER 35 U.S.C. §103(a):

The Examiner has maintained the rejection of all claims as obvious over the teaching of WO 96/34626 (Wheeler et al.) in view of WO 92/16556 (Van Wijnendale et al.) and U.S. Patent No. 5,795,862 to Frank et al. Wheeler et al. has been cited as disclosing a pharmaceutical composition comprising tyrosine and an optionally modified allergen. Van Wijnendale et al. is cited as disclosing a pharmaceutical composition comprising a modified or unmodified peptide antigen and 3-DMPL as an adjuvant. Frank et al. has been cited as disclosing a therapeutic composition for use in desensitization therapy, the composition containing at least one isolated flea saliva protein allergen, an adjuvant, and a carrier. The Examiner concludes that the combination of these teachings renders the pending claims obvious. Applicants continue to disagree.

The present invention concerns a pharmaceutical composition comprising tyrosine, an allergen or allergen extract, optionally modified by reaction with a cross-linking agent, and 3-DMPL. The invention is based on the important observations that 3-DMPL can enhance the TH_1 over TH_2 directing properties of administered allergens and that the adjuvant combination of tyrosine and 3-DMPL is surprisingly synergistic.

Wheeler et al. discloses a pharmaceutical composition comprising tyrosine and a polymerised (optionally modified) allergen. The application does not disclose or discuss 3-DMPL, a fact acknowledged by the Examiner on page 4, item 6, third paragraph, of Paper No. 11.

Van Wijnendale et al. discloses a novel form of gp160 and a vaccine formulation containing gp160 and 3-DMPL. The application teaches that, in the context of the prophylactic and therapeutic treatment of HIV infection, 3-DMPL is able to stimulate both arms (neutralising antibody and effector cell mediated immunity (DTH)) of the immune system (page 8, fourth complete paragraph). On pages 27 to 29, Van Wijnendale et al. describes experiments with an oil and water emulsion vaccine formulation containing the antigen rgp160 and 3-DMPL. The results indicate that the adjuvant formulations are able to induce a specific T cell response and that the adjuvant formulations significantly improve humoral (neutralising antibodies) and effector cell mediated (DTH) immune response in primates. Critically, however, **the application does not teach or suggest that 3-DMPL is suitable for use in allergen formulations and certainly not in formulations comprising tyrosine and optionally modified allergens.**

US 5,795,862 is aimed at the treatment of animals such as cats and dogs, more specifically allergic dermatitis in these particular animals. Claim 25 concerns a therapeutic composition comprising candidate flea saliva proteins, an excipient, an adjuvant, and a carrier. However, there is no mention of 3-DMPL nor of tyrosine in this document.

To establish *prima facie* obviousness, two basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable likelihood of success, view in light of the prior art. *Brown & Williamson Tobacco Corp. v. Phillip Morris Inc.* 229 F.3d 1120, 56 USPQ2d 1456, 1459 (2000) citing *In re Dow Chem.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Furthermore, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In the present instance, none of the cited documents contain any disclosure that would lead a skilled person to seek the teaching of the other. Moreover, as far as applicants are aware, there is no knowledge generally available to one skilled in the art that would motivate one of ordinary skill in the art to combine these references.

In particular, a person skilled in the art seeking to improve an allergen formulation, such as that disclosed in Wheeler et al., would take no relevant teaching from a document such as Van

Wijnendale et al. that is concerned solely with a vaccine formulation designed to combat a specific virus.

In normal individuals, T cells differentiate and produce cytokines that result in cell immunity and production of IgG antibody by B lymphocytes. In contrast, in allergic individuals a separate T cell differentiation pathway occurs and the resultant TH_2 cells produce a different set of cytokines that stimulate B cells to produce IgE antibody. Thus, allergy is due, in part, to an imbalance of the immune system in which there is a predominance of allergen specific TH_2 cells over TH_1 cells leading to abnormally high IgE antibody levels and inflammatory responses. Therefore, a goal of allergy treatment is to switch the abnormal T cell response of an allergic patient from a predominantly TH_2 driven response to a more pronounced TH_1 profile.

Human TH_1 cells develop in response to intracellular bacteria and viruses. Van Wijnendale et al. is concerned solely with vaccine formulations against the HIV virus and enhancing a specific T cell response (TH_1 response). **There is, however, a large difference between switching an unbalanced T cell response in the treatment of allergy and enhancing a specific T cell response in a normal non-allergic individual. There is no suggestion in Van Wijnendale et al. or any other prior art of record that formulations containing 3-DMPL might be able to switch the unbalanced predominantly TH_2 driven response of an allergic individual to a more pronounced TH_1 profile.** Therefore, there is no teaching or suggestion in Van Wijnendale et al. that 3-DMPL should be used in an allergen formulation.

Furthermore, although the Examiner has cited the disclosure in Van Wijnendale et al. regarding the ability of 3-DMPL to induce delayed-type hypersensitivity response (DTH), a TH_1 response, as evidence of the reference teaching the utility of 3-DMPL as an adjuvant, the cited disclosure actually teaches away from the use of 3-DMPL as an adjuvant in individuals not infected with a virus. This is because a DTH response is a cytotoxic response aimed at killing an invading virus and would certainly not be desirable in an allergic but otherwise healthy individual. **Thus, in fact, Van Wijnendale et al. teaches against the use of 3-DMPL in allergen formulations which are designed to treat people with an unbalanced immune response and not persons having an invading infectious agent.**

Thus, applicants submit that none of the references cited by the Examiner, nor the knowledge generally available to one of ordinary skill in the art, contain any disclosure that would motivate the skilled person to combine their respective teachings. In particular, applicants

submit that there is nothing in Van Wijnendale et al. that would motivate a person skilled in the art to include 3-DMPL in the allergen formulations disclosed in Wheeler et al. In fact, as discussed above, there are good reasons, e.g., the cytotoxic DTH response, why one of ordinary skill in the art would not include 3-DMPL in the allergen formulations disclosed in Wheeler et al. For these reasons, *prima facie* obviousness has not been established and applicants respectfully request reconsideration and withdrawal of the rejection.

Additionally, if there were some motivation to combine the teaching of Van Wijnendale et al. and Wheeler et al. existed, there is clear evidence of an unexpected result that would establish the nonobviousness of the present invention. A further and important aspect of the present invention is the observation that the TH_1 directing effect of the tyrosine / 3-DMPL combination is synergistic. The experiments using ovalbumin (XOA) in combination with tyrosine and 3-DMPL, described in examples of the present application, clearly disclose the unexpected synergistic effect of tyrosine in combination with 3 DMPL.

As stated under the heading Biological Activity on page 5 of the specification, TH_1 inducing activity in mice can be equated with the production of IgG2a and IgG2b antibodies and the TH_2 inducing activity with the production of IgG1 antibodies and IgE antibodies. An experiment was carried out in mice to demonstrate the profiles of the allergen specific antibodies to an exemplar allergen ovalbumin (XOA), a well-known allergen derived from chicken eggs. The results from the experiments are tabulated on page 6 of the specification. The results showed much higher levels of IgG antibody responses without any enhancement of the IgE response. Furthermore, the adjuvant combination promoted strong IgG2 responses indicative of a TH_1 directed response. The synergistic effect of combining 3-DMPL with insoluble tyrosine was seen as the induction of IgG2a and IgG2b responses to the adsorbed allergen whilst at the same time being least effective at inducing the IgE response compared to the other combinations.

Therefore, for the above-discussed reasons, applicants submit that the claimed invention is clearly nonobvious over the cited references, based on both the failure of the Examiner to establish *prima facie* obviousness and on the unexpected result of the synergistic, TH_1 directing effect of tyrosine and 3-DMPL. Reconsideration of the rejection is in order and is respectfully requested.

CONCLUSION

For the foregoing reasons, applicants submit that the claims are patentable over the art and satisfy all requirements of 35 U.S.C. §112. A Notice of Allowance is requested, and a prompt mailing thereof would be much appreciated.

If the Examiner has any questions concerning this communication, please contact the undersigned at (650) 330-0900.

Respectfully submitted,

Date: 2/19/02

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APPENDIX A

REDACTED SPECIFICATION AND CLAIMS INDICATING AMENDMENTS MADE

IN THE CLAIMS

Please amend claim 1 as indicated below. Text to be deleted is indicated as ~~deleted text~~, while added subject matter is underlined.

1. (Twice Amended) A pharmaceutical composition capable of selectively enhancing a TH_1 response comprising tyrosine, an ~~optionally modified~~ allergen or allergen extract, optionally modified by reaction with a cross-linking agent, and 3-DMPL.